

PATENT
1662/55002

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant : Shlomit Weizel et al.
Serial No. : 10/016752
Filed : October 30, 2001
For : NOVEL CRYSTAL AND SOLVATE FORMS OF
ONDANSETRON HYDROCHLORIDE AND PROCESSES
FOR THEIR PREPARATION
Examiner : Taylor V. Oh
Art Unit : 1625

Commissioner for Patents
P.O. Box 1450
Alexandria, Va 22313-1450

DECLARATION OF JUDITH ARONHIME UNDER 37 C.F.R. § 1.132

Sir:

I, JUDITH ARONHIME, Ph.D., of Harav Maor Josef 5a, Rehovot Israel,
declare as follows:

1. I have worked for Teva Pharmaceutical Industries, Ltd. ("Teva") since January 1991. Since then, I have been in charge of the solid state characterization laboratory at Teva. I received a Ph.D. degree from the Casali Institute of Applied Chemistry, the Hebrew University of Jerusalem in 1989. As head of the solid state characterization laboratory I have continued to study and use known techniques of solid state characterization and to use them to develop specific methods for the identification and quantification of compounds of interest. In our laboratory, we have characterized the solid state properties of over 30 drugs and drug products. I supervise eight coworkers.

2. Unless otherwise stated, I have personal knowledge of the solid state characterization of the materials discussed below: I either carried out or supervised these characterizations.
3. I am an inventor of U.S. Patent Application Serial No. 10/016752, captioned above, and am knowledgeable regarding its contents.
4. I have read the Office Action mailed January 6, 2003 and a copy of the English translation of Chinese Patent Application No. CN1113234A ("Wu Gousheng") that is the basis for the rejection of claims 1-4, 9, 19-23, 39-45, 49, 50, 52, 62, 67, 71, and 87-91 for lack of novelty.
5. Based upon my review of Wu Gousheng, it is my understanding that Embodiments A₁, A₂ and B produce ondansetron hydrochloride dihydrate ("compound X") by crystallization from water. In Embodiments A₁ and A₂, the dihydrate is dried in a dessicator over P₂O₅ under vacuum to yield ondansetron hydrochloride monohydrate.
6. I and my co-inventor Revital Lifshitz were prompted by the January 6, 2003 Office Action to study the solid state characteristics of the monohydrate products of Embodiments A₁ and A₂.
7. I received a sample of ondansetron hydrochloride monohydrate from Revital Lifshitz prepared, as I understand it, by the salification and recrystallization procedures described in Embodiment B of Wu Gousheng and vacuum drying as described in Embodiments A₁ and A₂.
8. I personally oversaw the performance of powder X-ray diffraction crystallographic analysis on the sample of ondansetron hydrochloride monohydrate I received. The instrumentation was a Scintag X-ray diffractometer, model X'TRA. Conventional CuK_α radiation was used. The X-ray pattern was acquired at a scanning speed of 3E per minute over a range of 2-40E two-theta.
9. The powder X-ray diffractogram I obtained from the ondansetron hydrochloride

monohydrate crystals is attached as Appendix A. Figure 1 of our patent application is reproduced in Appendix B. Figure 1 is a powder X-ray diffraction pattern of the ondansetron hydrochloride Form A described in our patent application.

10. Having compared the two diffractograms, I have concluded they were taken from samples of the same crystalline form of ondansetron hydrochloride. I base my conclusion on the correspondence of peaks along the x axis of the diffractograms. In particular, I refer to the peaks in Appendix A whose maxima were reported by the instrumentation to be at *12.4, 17.1, 18.3, 19.2, 20.3, 21.0, 23.3, 24.3, 25.8, 27.2, 28.0 and 30.2E* two-theta. Of these, the italicized peaks correspond to peaks listed in the application at p. 6, lines 7, 8, as occurring at 12.4, 17.0, 18.3, 19.2, 20.3, 20.9, 24.1, 25.8, 28.1 and 30.3 ± 0.2 degrees two-theta in the PXRD pattern of ondansetron hydrochloride Form A. I also noted that the relative intensities of these peaks in the two diffractograms appears to be in good agreement which further corroborates the identity between the two samples.
11. I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the application or any patent issuing thereon.

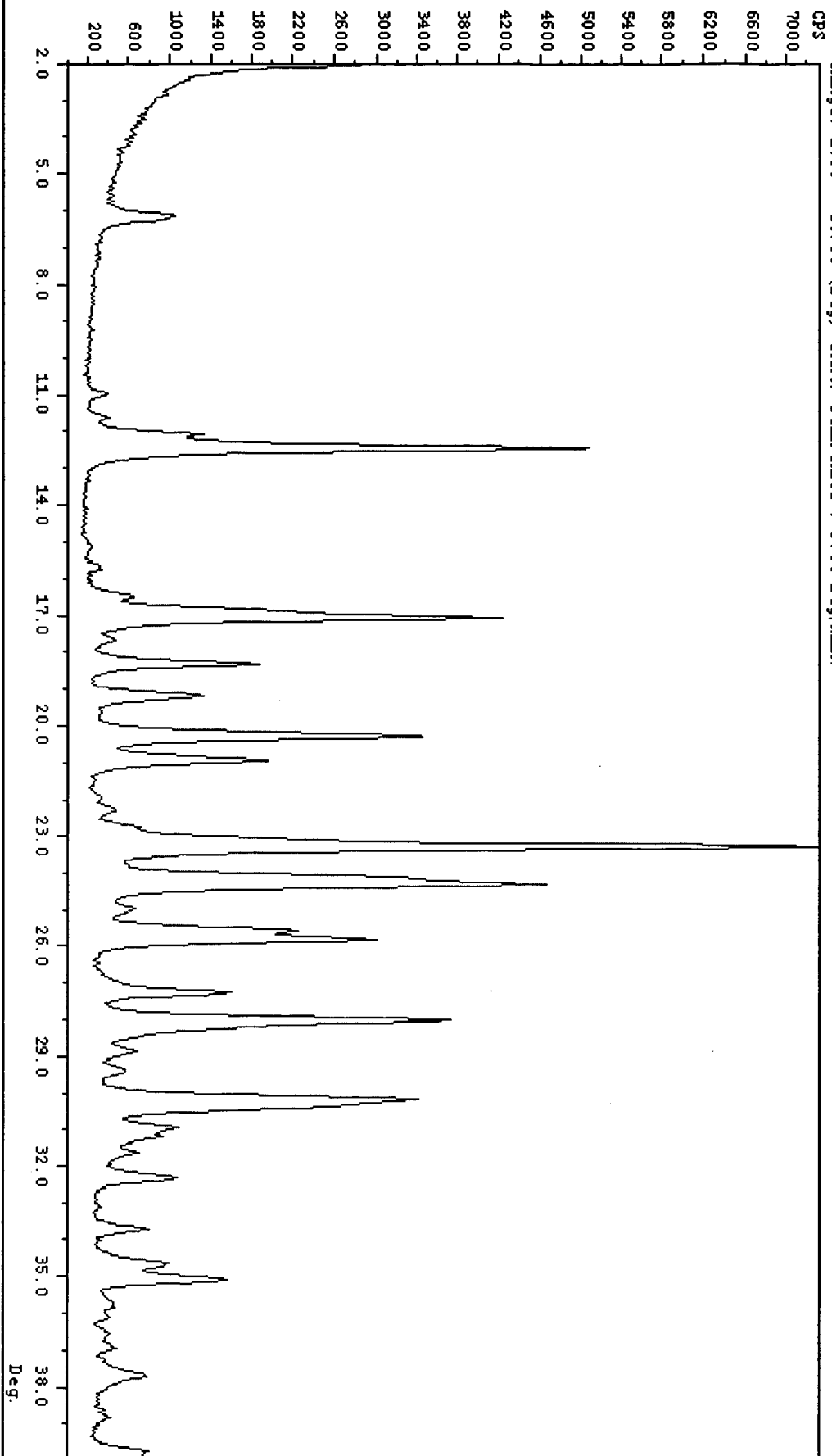
Dated: 24. 6. 03

Signed: 
Dr. Judith Aronhime

File: 0MD LB-438-2-III SHQ , ID: Analyst: Brran.

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Range: 2.00 - 40.00 (Deg) Cont. Scan Rate : 3.00 Deg/min.



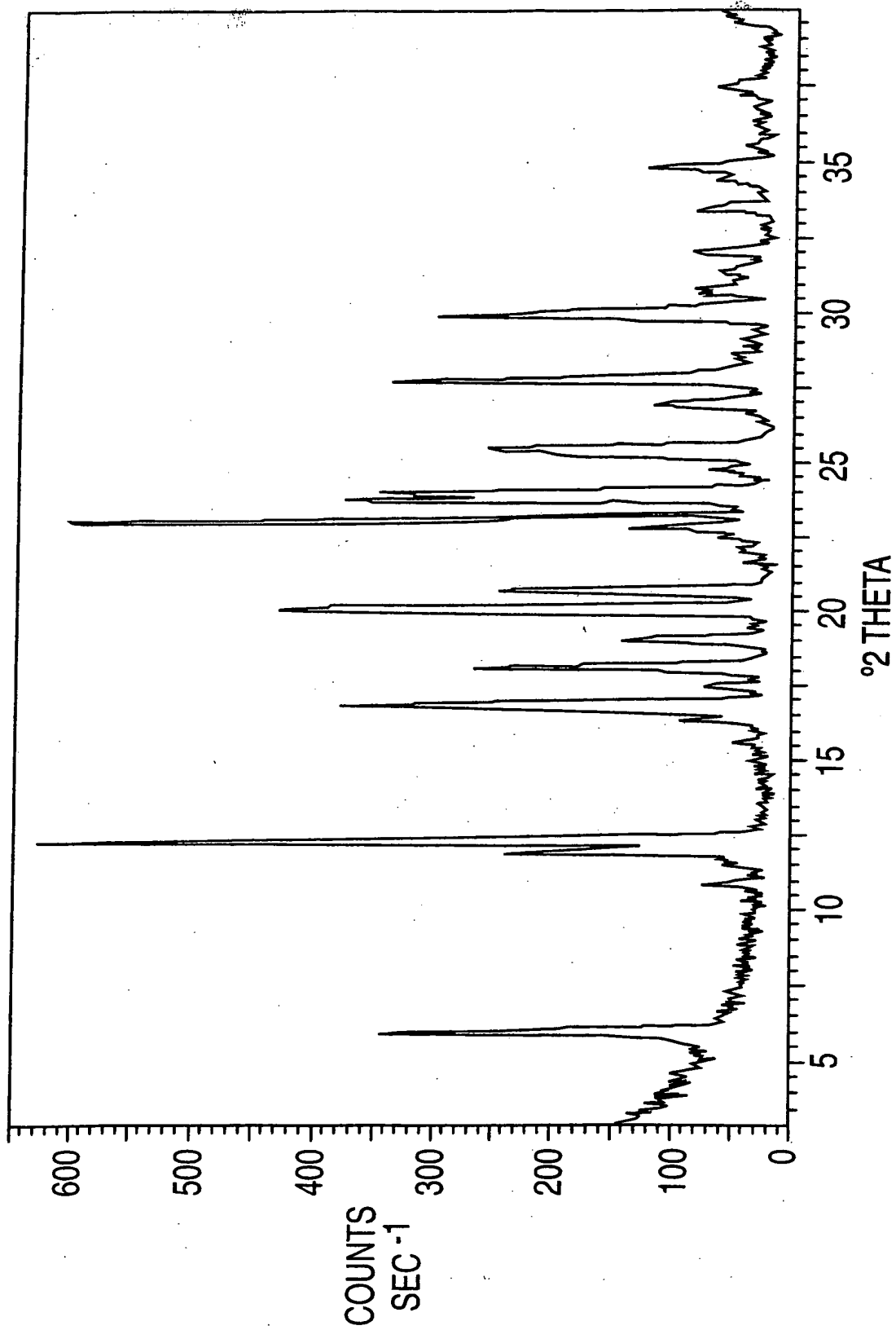


FIG. 1